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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/700,491	11/05/2003	Ali Amara	03495.0300	6283

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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	PAPER NUMBER
1648	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/700,491	AMARA ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,26-34,72,73,76-78,81-91,94,95 and 102-105* is/are pending in the application.

4a) Of the above claim(s) *31,72,73,76,77,86,90,91,94,95 and 102-104* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,26-30,32-34,78,81-85,87-89 and 105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/27/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and response filed November 27, 2006 is acknowledged and entered. It is acknowledged that a complete response was filed September 7, 2006, however, Applicant re-submitted the response after having viewed in PAIR that the response was not scanned in properly. The examiner notes that all of the documents were scanned in, however, they were mislabeled in the image file wrapper, thus PAIR did not display the documents properly.

Claims 23, 26-30, 32-34, 78, 81-85, 87, 88, 89 and 105 are under examination. Claims 23, 26-34, 72, 73, 76-78, 81-91, 94, 95 and 102-105 are pending. Claims 31, 72, 73, 76, 77, 86, 90, 91, 94, 95 and 102-104 are withdrawn from consideration, being drawn to non-elected subject matter.

Claims Summary

2. The claims are drawn to a method of treating Dengue virus infection of a human. The method comprises administering to a human a molecule that specifically binds to the DC-SIGN receptor, wherein said molecule inhibits the binding of the Dengue virus to the DC-SIGN receptor. By inhibiting binding, the Dengue virus infection in the human is treated. The treatment of the human for Dengue virus infection encompasses a method that imparts therapeutic benefit to the human such that some aspect of the disease is improved. The molecule that specifically binds to the DC-SIGN receptor is an antibody, more particularly a monoclonal antibody, even more particularly, a humanized antibody.

Claim Rejections - 35 USC § 112

3. The rejection of claims 23-30, 32-34, 78-85, 87-89 and 96-100 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention, is moot with respect to the cancelled claims, and withdrawn with respect to claims 23, 26-28, 32-34, 78, 81-83 and 87-89 in view of Applicant's amendment and persuasive arguments.

However, claims 29, 30, 84 and 85 remain rejected under 35 U.S.C. 112, second paragraph, and new claim 105 is rejected, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The claims are drawn to methods wherein the molecule that specifically binds to the DC-SIGN receptor comprises a binding moiety of the Dengue virus effector molecule, wherein the binding moiety specifically binds to the DC-SIGN receptor. It is unclear how the molecule that binds the DC-SIGN receptor is also a binding moiety of the Dengue virus effector molecule. For example, if the molecule that binds the DC-SIGN receptor is an antibody, then how is the antibody also a binding moiety of the Dengue envelope glycoprotein? Does the antibody bind both the DC-SIGN receptor and the Dengue envelope glycoprotein? If so, then how can the antibody be a monoclonal antibody? Clarification is requested.

4. The rejection of claims 23, 26-30, 32-34, 78, 81-85, 87, 88, 89 and 105 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to

make and/or use the invention. The claims are drawn to a method of treating a Dengue virus infection of a mammal comprising, administering to the mammal a molecule that binds to the DC-SIGN receptor.

The method claims are non-enabled for their asserted ability to treat or inhibit a Dengue virus infection *in vivo*. Methods of treatment and *in vivo* inhibition are not adequately enabled by the specification such that one of skill in the art would be equipped to practice the claimed methods.

The breadth of the claims is unreasonable, encompassing the inhibition of binding between Dengue virus and a human's dendritic cells, in a human already infected with the virus. The nature of the invention is the inhibition of Dengue virus via blocking entry of the virus into dendritic cells by preventing a Dengue viral molecule (such as envelope) from binding DC-SIGN.

The state of the art surrounding DC-SIGN and Flavivirus infection is that *in vivo* experiments have demonstrated a relationship between DC-SIGN and flavivirus envelope protein. Navarro-Sanchez *et al.* (*EMBO reports*, 2003, 4(7):723-728) discloses that DC-SIGN is essential for the productive infection of human dendritic cells by mosquito-cell-derived dengue viruses. Navarro-Sanchez *et al.* demonstrated this by inhibiting viral infection by anti-DC-SIGN antibodies and by the soluble tetrameric ectodomain of DC-SIGN (abstract). Navarro-Sanchez *et al.* discloses that the relevance of this discovery remains to be tested *in vivo*.

The level of skill in the art is high, evidenced by those of skill in the prior art.

The level of predictability in the art is low because the mechanism described in this invention is novel, and thus *in vivo* experimentation is required to determine whether *in vitro*

results reflect *in vivo* performance. As outlined previously, the Centers for Disease Control (CDC) reports that there is no vaccine for Dengue virus and that efficacy trials in humans have yet to be initiated as of the year 2003 (see website printout, page 4, "Future Outlook" section). Leyssen *et al.* (*Clin. Microbiol. Rev.* 2000, 13(1):67-82, herein, "Leyssen") confirms that there are no vaccines or treatments for Dengue virus (page 72, column 1, first full paragraph). Leyssen teaches that little is known about flavivirus entry and cell receptor (page 73, columns 1 and 2, bridging paragraph). Regarding Dengue virus, Japanese encephalitis virus and tick-borne encephalitis virus, Leyssen discloses that there are no drugs yet available (page 76, column 2, last paragraph). Men *et al.* (*J. Virology*, 2004, 78(9):4665-4674) also confirms that there are no vaccines for Dengue virus (abstract).

The specification does not provide guidance for inhibiting virus entry *in vivo*. If one of skill in the art were to treat a flavivirus infection, given the claimed methods and specification, one would not know what dosage of antibody, for example, should be used for binding DC-SIGN. Given the abundance of dendritic cells in an individual, one would have to consider what dosage of antibody would be appropriate for binding a significant number of dendritic cells such that the virus (already present in the body) would be inhibited. Applicant has not taught what effective amount of antibodies would result in a therapeutic benefit for the patient (an improvement in a symptom). Given the fast-acting viral pathology of Dengue virus, one would need to know the effective amount and frequency that would inhibit the binding of virus to dendritic cells.

Furthermore, regarding *in vivo* methods, which rely on generally unpredictable mechanisms, "The amount of guidance or direction needed to enable the invention is inversely

related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See, *e.g.*, *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a 'specific and useful teaching.' The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction (MPEP 2164.03).

Further, in *Rasmusson v. SmithKlineBeecham Corp.*, 75 USPQ2d 1297-1303 (CAFC 2005). The court states, "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the inventor would be rewarded the spoils of the party who demonstrated the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

Pharmaceutical therapies in the absence of *in vivo* clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, *i.e.* such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the

protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for *in vivo* therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

The working examples include *in vitro* binding inhibition of *Flaviviridae* virus. While this data is useful for demonstrating that there is relationship between DC-SIGN and flaviviruses, the data cannot be extrapolated to methods of improving the symptoms of any and all mammals infected with a flavivirus.

Given the breadth of the claims, the nature of the invention, the state of the prior art, the level of skill in the art, the low level of predictability, the lack of guidance and working examples, it would require undue experimentation to use the claimed invention as claimed. Further experimentation is required before *in vivo* applications are adequately enabled. Given this new mechanism of virus inhibition, one of skill cannot predict the *in vivo* results with any degree of certainty. Therefore, the claims are not enabled by the specification.

Response to Arguments

5. Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

- Applicant asserts that the statement in Navarro-Sanchez *et al.* regarding the requirement for the relevance of the DC-SIGN receptor to be tested *in vivo*, is merely

reflective of the ordinary prudence of scientists to not overstate what they have actually proved. Applicant argues that they need not prove beyond all doubt that their invention is commercially viable.

- In response to Applicant's arguments, the Office understands that Applicant does not need to prove beyond all doubt that their invention is commercially viable. However, Applicant does need to provide one of skill with the necessary information to perform the claimed methods with some expectation of success. Based on Applicant's *in vitro* data and limited experiments, one of skill in the art would not expect anti-DC-SIGN antibodies to bind DC-SIGN *in vivo* such that Dengue virus is inhibited or Dengue infection is treated. For Applicant to attempt to regard the statement of Navarro-Sanchez *et al.* about how *in vivo* studies are needed, as prudence only, is not acceptable proof that one would essentially ignore the statement of Navarro-Sanchez *et al.*

- With regard to the level of predictability, Applicant asserts that the information and teachings in the specification enable one to practice the invention as claimed. The obstacles that the examiner raised in the rejection with regard to predictability are determinations that are routine in the art. Applicant argues that the skilled artisan would be able to determine the dosages of antibodies necessary to inhibit Dengue virus entry. Applicant asserts that the skilled artisan would conduct *in vitro* studies, followed by studies in rats, and ultimately in humans to determine the amount of antibodies required to inhibit Dengue virus entry. Applicant asserts that this is the ordinary course of taking a discovery and commercializing it. Applicant asserts that

the Office's citation of articles that reflect the current state of the art with regard to Dengue treatments does not take into consideration the inventors' discovery and improvement on the state of the art.

- In response to Applicant's assertions, the more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. In this case, novelty of the invention renders it unpredictable when extrapolating *in vitro* findings to *in vivo* treatments and effects in humans.
- An obstacle for which Applicant has failed to provide adequate guidance is how to practice the claimed methods given the fast-acting viral pathology of Dengue virus. Once one is informed that they are infected, one would need to know the effective amount of antibodies required to inhibit the binding of virus to dendritic cells. One would not have time to do "routine experimentation" in order to determine the effective dosage required. Since some patients with Dengue progress rapidly, and some do not, dosages of antibodies is critical to practicing the invention.
- Another obstacle for which Applicant has failed to provide adequate guidance is how the complexes of antibodies and dendritic cells affect other cellular pathways. If the antibodies bind DC-SIGN on the dendritic cells, the dendritic

cells may be inhibited from effectively interacting in other critical cellular pathways. Applicant has not provided guidance on how the administration of antibodies to self-proteins will affect other components in the body.

- Applicant argues that claim 78 recites, "inhibiting entry of a Dengue virus into the cell of a human", and "wherein entry of the Dengue virus into the cell of the human is mediated at least in part by binding of a Dengue virus effector molecule on the Dengue virus to the DC-SIGN receptor on the cell of the human." Applicant asserts that the method does not require a specific therapeutic outcome, but rather a mechanistic one.
  - In response to Applicant's arguments, the claims encompass the inhibition of entry of a Dengue virus into the cell of a human. This is an *in vivo* method, which requires that the antibodies (or other molecules) bind to DC-SIGN in a human. Although, as Applicant notes, no therapeutic outcome is recited, the antibodies must be capable of binding to DC-SIGN such that virus entry is inhibited. Applicant has not demonstrated that the antibodies will remain viable long enough to produce the desired effect, *i.e.* such as proteolytic degradation, immunological inactivation due to an inherently short half-life of the antibody. Without *in vivo* evidence in an acceptable animal model to show that Applicant's anti-DC-SIGN antibodies will be able to bind DC-SIGN *in vivo*, one of skill in the art would have no basis to expect that the antibodies will bind DC-SIGN *in vivo* and block Dengue virus entry into DCs.

In conclusion, given the breadth of the claims, the nature of the invention, the state of the prior art, the level of skill in the art, the low level of predictability, the lack of guidance and working examples, it would require undue experimentation to use the claimed invention as claimed. Further experimentation is required before *in vivo* applications are adequately enabled. Given this new mechanism of virus inhibition, one of skill cannot predict the *in vivo* results with any degree of certainty. Therefore, the claims are not enabled by the specification.

Conclusion

6. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Stacy B. Chen 7/07

STACY B. CHEN
PRIMARY EXAMINER